Ethical and Legal Issues in Genetic Epidemiology

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INTRODUCTION

Since the discovery of recombinant DNA techniques in the 1970s, the identification of disease-related genes has rested on epidemiologic data (1, 2). The implications of gene identification for research subjects, for the transition to clinical practice, for clinical practice itself, and, finally, for society at large form the basis of this review. The ethical issues inherent in genetic testing have been widely discussed (3–6), as have the ethical issues in epidemiology (7), but little attention has been focussed on the specific ethical issues that arise in genetic epidemiology. In addressing genetic epidemiology, the emphasis of this review will be on topics of current interest, and often controversy, regarding the development and implementation of genetic testing and intervention technologies. We hope it will become clear that people considering genetic tests or treatments need reliable information—much of it based on epidemiologic studies—on which to make decisions, and society needs to develop measures to prevent the misuse of genetic testing and genetic information.

EPIDEMIOLOGY AND ETHICS

For over a century, researchers interested in the genetic characteristics of populations have been influential in the scientific and policy realms. As part of the earlier eugenics movement, researchers studied extended families looking for traits then considered to be inheritable, such as pauperism (8–10). Their results—which appeared to indicate the genetic inferiority of certain social and ethnic groups—served as the basis for laws mandating sterilization and governing who could immigrate into the United States (10, 11). Although clearly influenced by a political ideology, the researchers described their underlying goals as benefiting individuals by preventing the birth of people who would suffer due to their disabilities, and benefiting society by saving the money for caring for such individuals.

The controversial roots of population genetics in this country make analysis of ethical issues in contemporary practices particularly important. The current goals of genetic epidemiology are to identify disease-causing alleles to give individuals an increased number of choices to avoid or prevent genetic disease. Based on genetic information about disease susceptibility, individuals may choose, for example, to engage in preventive strategies (when available), to avoid environmental triggers to disease, or to avoid bearing affected children. At every juncture in the research and clinical enterprises, though, epidemiologists are faced with ethical issues. These include concerns about the manner of recruiting subjects, the age of potential subjects, confidentiality of research information, commercialization of research, the validity of resulting tests, the manner in which tests are offered to individuals and results communicated, and the impact of genetics on society at large.

The ethical issues confronting epidemiologists in the genetics field are particularly profound. While many epidemiologists work with sensitive and private medical records, genetic epidemiology research is different because if often involves testing, and thus creates genetic information about individuals and groups that did not exist before. That information can have a significant psychologic impact on the subject, can result in discrimination against the subject, and can serve as the basis for major decisions, such as a decision to terminate a pregnancy or undergo prophylactic surgery.

In genetics, the transition of a testing technology from research to practice occurs rapidly. Rather than working exclusively within the research setting, epidemiologists are increasingly drawn into decision-making about when a particular test is ready for clin-
ical use. In addition, the epidemiologists who are involved in studies that help localize a gene may be listed as a co-inventor on the resulting patent and thus have a commercial interest in any diagnostic tests or treatments performed with respect to that gene. Along with their multiple roles, epidemiologists have multiple responsibilities. They must concern themselves not only with the impact of their activities on research subjects, but also the impact of the resulting tests in the clinical setting and on society at large.

RESEARCH

The identification of a disease-related gene is often the first step in developing tests to detect those who carry disease-causing or susceptibility-conferring alleles and, then, to find interventions to prevent disease or reduce its burden in those at risk. The conduct of this research raises questions regarding the appropriate recruitment of subjects, the disclosure of research results to subjects, the confidentiality of the data collected, including biologic material, and the commercialization of such material.

Recruitment

The chromosomal location and ultimate identification of disease-related gene loci requires the participation of many people in relatively few large pedigrees or of a few affected relatives (e.g., sib-pairs) in many small families (2). Consequently, some element of coercion—either by relatives who are eager to participate or by investigators eager to recruit additional relatives—is possible. If the proband is used to recruit, he or she may have a personal stake in the research findings and may exert undue pressure on the relatives to enroll. On the other hand, the proband may be reluctant to contact relatives (12). When an investigator recruits family members directly, however, they may feel that their privacy has been invaded and, when they are contacted through their personal physicians, they may feel their health care will be compromised if they do not participate. The Office of Protection from Research Risks guidebook states that institutional review boards (IRBs) “must ensure that the recruitment plan minimizes the possibility of coercion or undue influence” (13, p. 5-44).

The issue of recruitment has become controversial in the context of the Human Genome Diversity Project, an effort to compare genomes of different ethno-cultural groups worldwide, as western values about science and about individual decision-making are not shared by some of the cultures being studied (14). Based on past experience, indigenous groups fear that blood will be collected without consent for future use and that they will not benefit from participating. Various advisory bodies to the Human Genome Diversity Project are currently developing guidelines for appropriate recruitment of subjects, and a National Academy of Sciences Committee is addressing the scientific and ethical implications of the project.

Disclosure of research results

When and if to disclose results to participants in research has long been a subject of debate. The issue arose in linkage studies for breast cancer when a healthy subject in a high risk family told investigators that she planned a prophylactic mastectomy. The research protocol had not provided for disclosure of results to the subjects. Yet, since the results of linkage studies indicated to the investigators that she was not at increased risk for breast cancer, they broke with the protocol and informed her of the results, thus allowing her to avoid potentially unnecessary surgery (15). Other researchers may also be tempted to disclose findings prematurely when research participants make a compelling claim that the information is of immediate use to them (for example, in a surgical decision or a decision whether to carry a pregnancy to term). Despite the seemingly compelling nature of a research subject’s request, there are a variety of reasons why researchers should not provide individual results to subjects before a study is completed. The validity of the results requires confirmation (12), and revealing them prematurely might lead a subject to take drastic, inappropriate action. Research projects that have not been designed to include disclosure of results may not have appropriate adjunct services available, including referral for genetic counseling. These deficiencies are likely to be magnified by the fact that once one family member has received her results, others (who perhaps have given the matter less careful thought) may want their results as well. Moreover, research projects that do not intend to provide results are not required to meet quality assurance guidelines that clinical laboratories do, and thus they may not be able to assure the quality of their testing procedures. Even if the test is one for a disorder in which corrective treatment is available, the fact that the research test might not be adequately validated or quality controlled could lead to individuals receiving treatment unnecessarily. It would be preferable for investigators to communicate their plans for informing, or not informing, potential participants at the outset, and not deviate from that position. If they plan to inform research subjects, they should assure the validity of the test.
Confidentiality

Information collected in genetic research is highly sensitive, often revealing future risks of disease not only to subjects but to their relatives (16). Some have argued that genetic information requires greater protection than other types of personal information, and laws have been introduced to protect its privacy in both research and practice settings (17). A number of authors and organizations have urged greater use of certificates of confidentiality by investigators (16, 18, 19). These certificates, which are granted by the US Department of Health and Human Services, protect sensitive research data (and only research data) from subpoena by any civil, criminal, or legislative proceeding. However, research data in the patient’s medical record, or even the statement in that record that a patient is a subject in research, is not protected.

The data in many genetic studies include participants’ DNA or the tissue, culture, or cultured cell lines from which DNA can be extracted. (In this section, the term “DNA” includes both; the person from whom DNA is obtained is referred to as the “source.”) Once collected for one research objective, DNA may be used for many additional types of research. Policies on who shall have access to stored DNA and under what circumstances informed consent of the source is needed are inconsistent. Weir and Horton (20) collected 103 informed consent forms that were given to participants in genetic research. Only 23 explicitly asked for consent before they stored DNA. Of those 23, the informed consent forms of the vast majority did not mention the length of storage, policies for withdrawal of DNA, and whether the individual or third parties would have access to the results of testing of the sample (21).

Increasingly, DNA is being “banked” for future analysis (22, 23). In a 1994 survey of DNA diagnostic laboratories, 84 of 93 respondents indicated that they were storing DNA with identifiers. Twenty-nine of these laboratories had no written policies regarding contacting or recontacting the source, or on who would have access to DNA and DNA test results. Forty-five laboratories had no type of written agreement with the source (24).

There is widespread agreement that consent is needed for additional genetic research in which the source’s identity will be retained, thereby permitting recontact either to get more information or to notify the subject of a potential risk of future disease. Some subjects would object to the research, would not be interested in providing more information or learning more about their risks (for example, whether they will get an untreatable disease like Huntington), or would be concerned about breaches of confidentiality that could harm them (for example, being denied health insurance; once informed of findings, they would be legally obliged to disclose on subsequent insurance forms that they had undergone testing). For these reasons, a strong case can be made that the consent should be for each specific research use. In contrast, several societies of pathologists maintain that “where identity can be determined . . . research using the specimen should be permitted under the general consent procedure when IRB-approved confidentiality and security polices are operational” (College of American Pathologists, Northfield, Illinois, 1996, unpublished document). Under “general consent,” the type of research or who would conduct it is not stipulated.

Although there is little disagreement about the appropriateness of research use of previously collected samples from which all identifiers have already been stripped, debate emerges about obtaining consent before anonymizing already-existing samples or samples to be collected in the future. To fail to do so when an investigator has the opportunity affronts the source’s autonomy, particularly if subjects might object to the type of research that will be done (18). If, however, a sufficient proportion of people declined to consent to anonymizing their samples, bias might skew the results, for example, in giving erroneous data about allele frequencies.

A National Institutes of Health (NIH)-Centers for Disease Control and Prevention workshop concluded that if the type of research proposed by the investigator “. . . was agreed to by the source at the time the sample was obtained, then there is no need for further consent [before anonymizing], although the IRB may choose to require that the investigator inform the sources . . .” (18, p. 1791). For specimens collected as part of clinical care, the report recommends that consent be obtained before anonymizing, taking into consideration the difficulty of recontacting, whether use of the specimen for research will reduce or eliminate further clinical use (from which the patient might benefit), and whether “. . . the availability of effective medical interventions affects the appropriateness of pursuing anonymous research” (18, p. 1791). Implementation of this recommendation would represent a significant departure from the current handling of clinical pathology specimens which are anonymized without informed consent after clinical analysis and report are completed (25).

The workshop report and a statement by the American College of Medical Genetics (ACMG) recommend that when genetic research is anticipated on specimens that will be collected from now on, whether for clinical or research use, that patients/subjects should be informed of the type of research contempl-
plated in the future and their permission obtained for anonymizing samples. The American Society of Human Genetics believes this is necessary only when specimens are given to another investigator who might anonymize them (19). The pathology societies argue that clinical specimens left after all “work necessary for the patient’s care has been completed” can be anonymized and “be appropriately used for research under a general consent” (College of American Pathologists, Northfield, Illinois, 1996, unpublished document).

The major argument for not requiring consent is that no harm will come to the individual if the sample is analyzed when his or her identity is not known. Insurers, for example, would not be able to discriminate against that individual because they would not know his or her name. On the other hand, individuals may have valid reasons for why they do not want to participate in genetic research even if their samples have been anonymized. Such participation may violate their religious principles or may lead to discrimination against them not as individuals but as members of a group (for example, if, as a result of anonymous research, women were found to have a gene associated with lesser cognitive abilities). People who disapprove of the patenting of human genes may legitimately not want to have their samples used—even anonymously—in work that leads to gene patenting. And, with the recent possibility of mammalian cloning (26), some people may find it morally offensive to have their anonymous samples used in genetics research involving cloning.

Commercialization

The possibility of commercial profit from the patenting of genes and the development of genetic tests has created situations in which health care providers and researchers, including epidemiologists, may have interests that conflict with those of research subjects and patients. This possibility was underscored in the case of Moore v. Regents of the University of California (27). Moore, a patient with hairy cell leukemia, had his spleen removed at the University of California, Los Angeles, School of Medicine. He alleged that, at the time his spleen was removed, his physician knew that his cells were commercially valuable because the cells could produce lymphokines. When Moore later learned that his physician had patented a cell line made from Moore’s tissue without his knowledge or consent, he sued the physician and hospital for stealing his property and for failure to properly inform him. Although the California Supreme Court would not apply the label of “property” to his cells (and thus would not recognize the theft claim), the court held that the law requires that physicians disclose in advance of removing tissue whether there is a chance that they will pursue scientific or commercial research.

THE TRANSITION FROM RESEARCH TO CLINICAL PRACTICE

The relation between epidemiology and public health has often been closely intertwined (28–30); epidemiologists are not only interested in learning about causes of disease but in improving health once more is learned about causation. In genetics, this takes the shape of making genetic testing and screening available once genetic factors have been identified. The public will not be well-served, however, unless initial research findings are confirmed. Even then, the phenomena of genetic heterogeneity and incomplete penetrance may reduce the safety and effectiveness of genetic tests. Finally, the test must be demonstrated to have clinical utility.

Confirmation and generalizability

Scientists who located the Huntington disease (HD) gene generated controversy when they refused to make the probes available for clinical testing outside of IRB-approved investigative protocols (31, 32). Concerned about genetic heterogeneity, they insisted that it was necessary to demonstrate that linkage held in a large proportion of families with Huntington disease. Although linkage of the HD gene to chromosome 4 was confirmed, and testing for Huntington disease began at that point, early reports of linkage of a gene for bipolar-affective disorder to chromosome 11, and of one for schizophrenia to chromosome 5, were subsequently withdrawn or not confirmed (33, 34). One reason for these premature claims was failure of the investigators to recognize the high probability of chance associations when making searches for relatively small DNA segments (of the order of 100 kb) among an enormous genome (of 3,000 kb) (34). The premature use of these probes would have violated Gusella’s words for HD, been “no better than guesswork” (32, p. 21), leading to erroneous predictions.

Genetic heterogeneity and allelic diversity

Studies intended to localize and identify genes are usually limited to a small proportion of all people with the disease. There is always the possibility, as concerned the Huntington disease researchers, that, due to genetic heterogeneity, the gene locus that is implicated in some families does not play a role in other families with the same disease. Two gene loci have already been found for breast cancer susceptibility (35), and six for hereditary colon cancer (36).
The few mutations discovered in the identification of a disease-related gene may be just the tip of the iceberg of allelic diversity, that is, the number of different mutations at a gene locus that are associated with disease. In the first papers reporting identification of the cystic fibrosis transmembrane regulator (CFTR) gene, one mutation was estimated to account for about 70 percent of all mutations and, consequently, slightly less than 50 percent of all patients with this autosomal recessive disease. Over 600 mutations have now been reported to account for cystic fibrosis (37), but the number of CF mutations that can be detected by current technology accounts for only about 85–90 percent of all carriers. A NIH workshop and the American Society of Human Genetics concluded that unless approximately 95 percent could be detected, cystic fibrosis (CF) carrier screening should not be offered to populations (38, 39). There is widespread agreement that CF carrier testing should be available to families in which cystic fibrosis has occurred. A NIH Consensus Development Panel recently reviewed data on the natural history of cystic fibrosis, therapeutic advances, progress in detecting additional disease-related mutations, and the results of pilot screening programs. The latter found low demand for carrier screening except in pregnancy (40). The panel's recommendations include that "CF genetic testing" be offered "to couples currently planning a pregnancy, and to couples seeking prenatal testing. The panel (does) not advocate offering CF genetic testing to the general population" (41).

Penetrance

As the name implies, an inherited susceptibility mutation is not sufficient to cause disease. In many common diseases, other genetic and environmental factors must be present as well. For cancers in which alleles at single loci increase susceptibility, such as breast and colon cancer, somatic mutations in the homologous gene and at other gene loci are needed for malignant transformation (42–45). Among people with hypercholesterolemia, which is at least partly genetically-determined, environmental factors, such as smoking, increase the risk of myocardial infarction (46). If the inherited susceptibility allele is present but other factors are absent, the disease will not develop, that is, the allele is incompletely penetrant. Even in Mendelian diseases, the same inherited mutation may not always lead to symptoms, or the age at onset and the severity of symptoms may vary considerably (47).

The penetrance of alleles found in high-risk families selected for linkage and affected-relatives studies may be stronger than in the general population because of the presence of other inherited and shared environmental factors in these families (48). The need to establish population penetrance is exemplified in the following three disorders.

Breast cancer. The need for population-based data to resolve questions of penetrance is illustrated by recent studies of the 185delAG mutation at the BRCA1 locus in Ashkenazi Jewish women. Following a report (49) that about 1 percent of Ashkenazi Jews inherit this mutation, which increases susceptibility to breast cancer in high-risk families (50, 51), at least one laboratory began to offer testing to Jewish women regardless of family history (52). This policy has been criticized (53, 54). A major concern was that the risks of cancer in Ashkenazi Jewish women would prove to be lower than the estimates based on early studies of subjects with a very large number of relatives with cancer. A very recent population-based study among Ashkenazi Jews confirms this possibility (55). The risk of breast cancer by age 70 years was 56 percent (95 percent confidence interval 40–73 percent) in contrast to a much higher estimated risk of breast cancer, of approximately 85 percent by age 70 years among carriers of BRCA1 mutations in very high risk families (56). The risks of ovarian cancer were also lower than previously estimated. Among the 120 subjects who carried a BRCA1 or BRCA2 inherited susceptibility mutation, 31 did not report a family history. The number of their first-degree female relatives (at risk) was only slightly lower than among people with these mutations who had a family history of breast cancer (3.3 versus 3.7 female relatives); 18 percent of those without a family history had three female relatives over 40 years of age. The authors conclude that the variability in risk of cancer among carriers may be due "... to chance, to genetic and environmental modifying factors, or to both" (55, p. 1406).

The study did confirm the high frequency of two BRCA1 mutations in the Ashkenazi Jewish population (185delAG, 0.8 percent; 5382insC, 0.4 percent) and one BRCA2 mutation (6174delT, 1.2 percent) (55). The differences in risk of breast cancer to women before age 50 years between 185delAG (34 percent) and 6174delT (26 percent) were not as great as previously reported (57, 58).

A negative BRCA1 or BRCA2 test cannot provide women with much reassurance that they will not get cancer unless they have a relative with breast cancer who tests positive for an inherited susceptibility mutation.

Alzheimer disease. The probability of higher penetrance of a disease-associated allele in families with multiple affected members is illustrated by studies on the apolipoprotein E4 allele (ApoE4) and Alzheimer disease. Although no long-term, population-based prospective study has yet been reported, a number of
Hemochromatosis. Hemochromatosis is a disease of iron overload leading eventually to multiorgan failure. The iron accumulation can be prevented by periodic phlebotomy. Homozygotes for a single mutation may account for over 80 percent of Caucasian patients with hemochromatosis (64). Of 155 controls, 6.4 percent were carriers of this mutation (64), suggesting that approximately 0.1 percent of the Caucasian population should be affected if the allele is fully penetrant. Until we know the penetrance, routine screening for the single mutation, which may be the least expensive means of early detection, would be premature. Phlebotomy in homozygotes who may not develop iron overload could cause anemia.

Clinical utility

The ability to test for disease-causing or susceptibility-conferring genotypes is likely to precede the ability to treat effectively those who are found by testing to be at risk (65). For early-onset, severe Mendelian diseases, carrier testing gives parents at risk options of avoiding the conception of affected offspring. Carrier testing and prenatal diagnosis provide the option of avoiding the birth of affected offspring.

When treatments are available, predictive testing is sometimes undertaken before their safety or effectiveness have been established (66). At least two states, Colorado and Wisconsin, mandated the screening of newborns for cystic fibrosis at a time when the benefits of early detection had not been established (67). The recent Consensus Development Panel on Testing for Cystic Fibrosis did not recommend screening of newborn infants for the disease (41). Testing for rare genetic diseases has been mandated in some states only to be dropped because of low yields, high numbers of false positive test results, or failure to improve outcomes.

Testing for inherited susceptibility to breast cancer has started despite ignorance about the safety and effectiveness of interventions in women with positive test results. Mammography may have poor sensitivity in young women with a family history of breast cancer (67, 68), and may increase the chance of radiation-induced cancer. Prophylactic mastectomy may not remove all breast tissue; cancer in residual tissue has been reported occasionally (69). Prophylactic oophorectomy does not completely eliminate the risk of ovarian cancer (69). If genetic tests for susceptibility become established as routine care before the safety and efficacy of available interventions are established by randomized clinical trials or other less rigorous means, it will be extremely difficult to determine optimal management pathways (70).

Concerns for efficacy and quality assurance

Professional organizations have cautioned about the use of certain genetic tests in routine practice (71-73), but there is no legal mechanism for limiting use of these tests. Although genetic tests fall into the category of medical devices, which are subject to regulation by the US Food and Drug Administration, they are usually developed "in-house" by clinical laboratories and marketed as testing services. Although it has the authority to regulate devices marketed as services, the US Food and Drug Administration noted recently that "in-house" developed tests have not been regulated by the Agency (73).

Although every clinical laboratory must be certified by the Health Care Financing Administration under the Clinical Laboratory Improvement Amendments of 1988, neither the Amendments nor regulations pursuant to them have provisions for assuring the quality of predictive genetic testing (59, 74, 75). The College of American Pathologists jointly with the American College of Medical Genetics offers proficiency testing in the area of genetic tests to clinical laboratories, but no laboratory is compelled to participate (75). New York has a program for assessing the quality of laboratories providing genetic tests that applies to all laboratories providing testing to residents of New York State.

The decision to add tests to state-run or mandated newborn and prenatal screening programs rests either with state legislatures or with health departments. A recent survey of directors of genetic testing programs in all states revealed that while a few states consulted IRBs in the evaluation of protocols for screening and a few others had advisory committees, some with consumer representation, in many states the decision to add new tests was made without outside consultation (76).

CLINICAL PRACTICE

The inherently probabilistic nature of genetic test results, and the absence of proven therapy for those born with many genetic disorders, raise questions about the benefits and risks of genetic tests that enter routine practice. Some healthy people would decide not to have a genetic test if its predictive capabilities
were less than perfect. In the absence of therapy, people may be confronted with making difficult decisions about reproductive options, but even when these options are not used, and when therapy may be available but is very costly, psychologic and social issues arise, including communicating results to relatives and discrimination. The possibility of testing children raises additional concerns.

Informed consent

The uncertainty and risks of genetic testing argue for giving individuals sufficient information to decide, in an uncoerced way, whether or not to proceed with testing and requiring their informed consent for routine testing. The American College of Medical Genetics and the Institute of Medicine’s Committee on Assessing Genetic Risks have both made recommendations about the information that should be provided (62, 74). It includes the purpose and limitations of the test (e.g., possibility of false-positive and false-negative results and predictive value), and possible outcomes (62); alternatives to having the test; the severity, potential variability, and treatability of the disorder being tested for; and information about the subsequent decisions that will be likely if the test is positive (e.g., whether the person will have to make a decision about abortion) (74), as well as methods for communicating and maintaining confidentiality of results (62). Information should also be provided about any potential conflicts of interest of the person or institution offering the test (27). This would include whether the person or institution plans to do subsequent research on the sample, has equity holding or ownership in the company or laboratory offering the test, has a patent related to the test, or is dependent on test reimbursement to cover the costs of counseling (74).

Despite widespread agreement on the need for informed consent for genetic testing in clinical practice, there is controversy about the need for consent in newborn screening. With the exception of Maryland and Wyoming, virtually all states mandate screening (76). A few allow objections on religious grounds, but seldom are parents given the opportunity to object (77). As already discussed, not all tests mandated by screening programs have proven to be valid or beneficial, and some have been dropped. Even for those that are of clear benefit (phenylketonuria, congenital hypothyroidism, and sickle cell anemia), there may be reasons to favor informing parents in advance. Parents can then double-check to see that the test has actually been performed, which is especially important when infants are discharged within a day of delivery.

The Institute of Medicine’s Committee on Assessing Genetic Risks recommended that informed consent be obtained prior to newborn screening (74). Some in the public health community have objected on the grounds that obtaining informed consent is costly and that meaningful informed consent cannot be obtained within the limited budgets available (78). But research in Maryland on informing parents about newborn screening has found that it is possible to do so within limited budgetary and time constraints (79, 80).

Communicating results

In clinical practice, results of genetic tests will generally be reported to the people tested or their parents or guardians. Situations may arise in which people agree to be tested but do not want their results (e.g., relatives who agree to participate in linkage studies to establish the risk to the proband). Their preference should be respected.

One of the concerns in carrier screening (for autosomal recessive conditions) is the cost of informing all carriers of the results even though the vast majority of them will not be at risk of having an affected offspring because of the very small chance that they will mate with another carrier. Another concern is the stigmatization of carriers even though they will never manifest the disease (81). In one program, CF carrier screening is offered only to couples, and the results are reported only when both partners are carriers (82). Although efficient, this denies people knowledge of their carrier status and requires that they be screened again should they divorce and remarry, or if they doubt that the test was correctly performed. To avoid stigmatization, the Dor Yeshorim program screens young Hasidic Jews for traits of high frequency in the Jewish population (Tay Sachs, Gaucher). The results are stored under a code number and are not given to screenees. When marriage between two screenees is contemplated, they (or a matchmaker) can call the repository, giving only the pair’s code numbers. The repository will inform them only that a match is unadvisable on the basis of both specimens showing carrier status for the same recessive disorder (83).

Test uncertainty

Test uncertainty appears to be very important in peoples’ decision to undergo genetic testing. Tambor et al. (84) and Chase et al. (85) constructed an instrument to measure tolerance for test uncertainty; people were asked whether they would take a predictive test under varying conditions of sensitivity and positive predictive values. People who had low tolerance for test uncertainty (low sensitivity and/or low positive
predictive values) were almost four times less likely \((p=0.002)\) to decide to have a CF carrier test than those with high tolerance. Among individuals planning to have children, tolerance for test uncertainty had a higher odds ratio in predicting the decision to actually have a CF carrier test than perceived likelihood of being a carrier, fear of stigmatization, and age (all of which were also significant in multiple logistic regression). Educational attainment, attitudes towards prenatal diagnosis and abortion, and gender were not significant predictors. Given the importance of test uncertainty in their actual decision to have a test, data should be available to people considering testing on sensitivity and positive predictive value. Unfortunately, not only are the data not given but often they have not even been collected!

Some have argued that people have a right to know even when test validity and the implications of the results are uncertain \((86)\). Interestingly, women’s interest in testing for genetic susceptibility to breast cancer declines significantly as they learn more about the limitations of current tests, including their imperfect positive predictive value \((87, 88)\). One critic suggests it is paternalistic for scientists to deny testing outside of a research setting until all of the answers are in \((86)\). However, without either collecting information on the issues that people deem important, or informing them of what is not known, an informed decision cannot be made by individuals considering whether or not to undergo genetic testing.

**Psychologic and social risks**

As early as 1974, some geneticists were advocating that screeners should “...inform the participants about possible social and psychological embarrassments in case they are found to be heterozygotes” \((81, p. 275)\). Informing about risks is in keeping with the expectations of consumers as well. In a survey of people with genetic conditions in their family, 75 percent felt that “people need to know the risks of genetic tests in order to give informed consent” \((87)\). Lerman et al. recently reported psychologic changes in men and women offered results of investigative testing for inherited breast cancer susceptibility. Those who were told they were not carriers of detectable mutations showed a reduction in depressive symptoms compared with those who were told they were carriers of a BRCA1 mutation and those who declined receiving results. The latter two groups did not show changes. People without health insurance were the most likely to decline receiving their results \((89)\).

Discrimination in insurance and employment has been documented \((90–93)\). Several states have passed laws preventing insurance discrimination on the basis of genetic tests, but these do not apply to self-insured programs that are exempt from state legislation \((94)\). The Health Insurance Portability and Accountability Act of 1996 extends some protection to people covered by self-insured plans \((95)\), but does not prevent all health insurers from charging those with preexisting conditions (including genetic traits) higher premiums, which may price insurance out of the range of many individuals.

The fear that a person could be denied employment because of a genetic trait has been reduced as a result of the decision of the Equal Employment Opportunity Commission to extend the protection of the Americans with Disabilities Act to genetic traits \((96)\), but disabilities arising from genetic traits could still be excluded from employers’ health insurance coverage once people are hired if there is an actuarial basis for doing so and it is done for all people who would get the same disability \((96)\).

Pilot studies of cystic fibrosis \((40)\) lend credence to the recommendations that information about risks of anxiety, stigmatization, and discrimination should be part of informed consent. In one of the pilot studies that did not provide information about stigmatization or insurance risks, 11 percent of the subjects experienced concern over what others would think if the test were positive, and 30 percent said they would refuse testing if they knew the result would be given to insurers \((97)\). Because such factors are relevant to the individuals being tested, such information should be provided in advance of the test.

**Testing children**

When children undergo genetic testing, typically it is the parent who chooses whether to have the test and not the child. There is no widely accepted standard among physicians for making decisions about genetic testing of children \((97)\). A recent survey in the United Kingdom found that some laboratories currently perform genetic testing on children, including carrier testing and predictive testing \((98)\). Despite the fact that the International Huntington Association and the World Federation of Neurology have issued guidelines recommending that minors not be tested for Huntington disease, 53 percent of British pediatricians say they would test for the disorder upon parental request \((98)\). Some commentators suggest parents should be able to obtain genetic information about children even if there is no potential medical benefit to the child \((99)\). Others would restrict or prohibit such testing unless there is a
medical benefit (100). (One benefit would be avoiding periodic monitoring of children whose genetic test results are negative, as is the case in familial adenomatous polyposis.) The Institute of Medicine’s Committee on Assessing Genetic Risks recommended that “in the clinical setting, children generally be tested only for disorders for which a curative or preventive treatment exists and should be instituted at that early stage. Childhood screening is not appropriate for carrier status, untreatable childhood diseases, and late-onset diseases that cannot be prevented or forestalled by early treatment” (74, p. 276).

There are major psychologic implications when parents are allowed to learn their child’s genetic makeup. A joint American Society of Human Genetics/American College of Medical Genetics statement notes that “A child known to have a deleterious gene may be overindulged, rejected, or treated as a scapegoat” (101, p. 1236). This statement also notes, “Expectations of others for education, social relationships, and/or employment may be significantly altered when a child is found to carry a gene associated with a late-onset disease or susceptibility. Such individuals may not be encouraged to reach their full potential, or they may have difficulty obtaining education or employment if their risk for early death or disability is revealed” (101, p. 1236).

IMPLICATION OF GENETICS TO SOCIETY AT LARGE

In recent essays on epidemiology, Susser and Susser (102) and Pearce (30) note that epidemiology has moved away from a search for explanations of disease at the population level to a search at the individual level. Nowhere is the emphasis on individual risk factors greater than in genetic epidemiology. But the fascination with genetic explanations has extended well beyond epidemiologists. The popular press greets the discovery of disease-related genes with great fanfare, often exaggerating their health implications (103). Genes permeate the popular culture. In novels, movies, soap operas, and advertisements, a wide range of good and bad behaviors are attributed to inheritance (104). Nelkin and Lindee point out why such explanations are readily accepted by the public: “[they] can relieve personal guilt by implying compulsion, an inborn inability to resist specific behavior” (104, p. 145), and they can relieve societal guilt and give society an excuse to cut out social services by deflecting attention away from social and economic influences on behavior.

The emphasis on genetic causes leads to an approach that blames the victim and emphasizes the role of nonmodifiable genetic factors to the detriment of modifiable social and behavioral factors. Such an approach will have a small yield. No more than 5 percent of all cancer can be attributed to single inherited factors (105). The percentage is probably not much different for other common disorders as well.

Genes do contribute a much larger percentage to common disorders, not because of the inheritance of single alleles that markedly increase susceptibility, but because of the simultaneous presence of inherited alleles at several independently segregating loci and/or because of somatic mutations. Recognition of either of these phenomena would lead to other strategies than testing for genetic susceptibility. First, unless the alleles that must be simultaneously present have extraordinarily high frequencies, they cannot account for a high proportion of any common disease. For instance, if alleles at three different gene loci had to be simultaneously present to significantly increase the risk of a common disease, the chance of this happening would be one in a million even if each of these alleles had a frequency of 1 percent. The common diseases that society is concerned about occur much more often than 1 in a million. Second, at least for cancer, the deleterious effect of genes is much more likely to result from somatic than from germine mutations (106). The policy that makes sense here, and which is receiving increasing attention among epidemiologists (107), is the use of markers, such as DNA adducts, to indicate which environmental agents are capable of affecting basic molecular structure (by, for example, mutagenesis) and function in a large proportion of exposed individuals, and, once determined, to reduce exposure to those harmful substances.

CONCLUSION

Placing undue emphasis on the inherited factors in common diseases does not comport with scientific realities and may impede efforts to understand the complex causes of disease. The complicated nature of the genetic etiology of diseases creates a pressing need for research on the sensitivity and predictive value of genetic tests, the efficacy of efforts to prevent the occurrence of or treat the resulting disorders, and the development of adequate informed consent procedures.

REFERENCES

172 Holtzman and Andrews


from the Newborn Screening Committee of the Council of Regional Networks for Genetic Services. Screening 1996;4: 626–37.
99. Susser M, Susser E. Choosing a future for epidemiology. II.


